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BEFORE THE BOARD OF PATENT APPEALS AND INTERFERENCES

Paper No. 20031126

Application Number: 09/525,867
Filing Date: March 15, 2000
Appellant(s): YUE ET AL.

Susan Sather
For Appellant

EXAMINER'S ANSWER

This is in response to the appeal brief filed 7/30/2003.

(1) Real Party in Interest

A statement identifying the real party in interest is contained in the brief.

(2) Related Appeals and Interferences

Appellant's brief includes a statement that there are no related appeals or interferences known which will directly affect or be directly affected by or have a bearing on the Board's decision in the instant appeal.

(3) Status of Claims

The statement of the status of the claims contained in the brief is correct.

(4) Status of Amendments After Final

The Appellant's statement of the status of amendments after final rejection contained in the brief is correct.

(5) Summary of Invention

The summary of invention contained in the brief is substantially correct. However, it includes statements in regard to its utility which are appropriately found in the argument's section of the Brief and will be addressed in the Response to Arguments section of this Answer.

(6) Issues

The Appellant's statement of the issues in the brief is correct.

(7) Grouping of Claims

Appellant's brief includes a statement that all the claims on appeal stand or fall together.

(8) Claims Appealed

The copy of the appealed claims contained in the Appendix to the brief is correct.

(9) Prior Art of Record

Bork, Genome Research, 10:398-400, 2000.

Brenner, TIG 15:132-133, 1999.

Brenner et al., Proc. Natl. Acad. Sci. USA 95:6073-6078, 1998.

Broun et al., Science 282:1315-1317, 1998.

Seffernick et al., J. Bacteriol. 183(8):2405-2410, 2001.

Van de Loo et al., Proc. Natl. Acad. Sci. 92:6743-6747, 1995.

Witkowski et al., Biochemistry 38:11643-11650, 1999.

Hyslop et al., Genomics 37:375-380, 1996.

Arizmendi et al., FEBS Lett. 301:237-242, 1992.

Arizmendi et al., Swiss Prot accession number P42026, November 1, 1995.

Steiner et al., Toxicology Letters 112-113:467-471, 2000.

Rockett et al., Xenobiotica 29:655-691, 1999.

Nuwaysir et al., Molecular Carcinogenesis 24:153-159, 1999.

Rockett et al., Environ. Health Perspec. 107:681-685, 1999.

Lashkari et al., Proc. Natl. Acad. Sci. 94:8945-8947, 1997.

(10) Grounds of Rejection

The following ground(s) of rejection are applicable to the appealed claim:

Claim Rejections - 35 USC § 112 – Written Description

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Claim 31 is rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Claim 31 is directed to a genus of polynucleotides of any function comprising a naturally occurring polynucleotide sequence at least 80% identical to the polynucleotide sequence of SEQ ID NO: 9 over the entire length of SEQ ID NO: 9.

A sufficient written description of a genus requires that the specification describe the attributes and features of a sufficient number of species within the genus so that the described species are representative of the attributes and features of all members of the genus. A complete description of any species should include description of both the structure and function of the species. While the specification does not specifically define the intended meaning of the term "naturally-occurring", one of skill in the art would interpret such term as meaning "as found in nature", which is the case with allelic variants. Thus, the claimed genus will encompass allelic variants of the gene of SEQ ID NO: 9 as well as many species homologs of the gene of SEQ ID NO: 9 and their corresponding allelic variants. The claimed genus may also encompass other human genes and their allelic variants since the occurrence of multiple loci encoding highly related genes is commonly found in the human genome. The specification defines an "allelic variant" (pages 6-7) as an alternative form of the gene which may result in at least one mutation in the nucleic acid sequence. Alleles may result in altered mRNAs or polypeptides whose structure or function may or may not be altered. This definition does not provide any specific information about the structure of naturally occurring variants (alleles) of the polynucleotide of SEQ ID NO: 9 as recited in the claim (i.e. where are the regions within which mutations are likely to occur), nor does it provide any information as to the functional effects of the mutation. The specification is completely silent as to the mutational sites that exist in nature and there is no description of how the structure of the polynucleotide of SEQ ID NO: 9 relates to the structure of any naturally-occurring variant as claimed. The general knowledge in the art concerning a naturally occurring variant, such as an allele, does not provide any indication of how a naturally-occurring variant is representative of unknown naturally-occurring variants as other species clearly differ in structure in some respect and often differ drastically in function. In the case of alleles, there is no indication in the art that would suggest that the structure and function of one provides guidance to the structure and function of others.

In addition, while the specification provides the structure of the polynucleotide of SEQ ID NO: 9 and asserts a function for the polypeptide encoded by the polynucleotide of SEQ ID NO: 9, the specification fails to disclose all the functions of other polypeptides encoded by a genus of polynucleotides comprising a naturally occurring polynucleotide sequence having at least 80% identity to the polynucleotide sequence of SEQ ID NO: 9 over the entire length of SEQ ID NO: 9. The claimed genus has the potential of being highly functionally diverse. The genus would encompass polynucleotides encoding a PSST subunit of the NADH:ubiquinone oxidoreductase complex, such as the polynucleotide of SEQ ID NO: 9, as well as polynucleotides encoding proteins of any function. In addition to the lack of description of all the functions for the genus of polynucleotides encompassed by the claim, it is also noted that the specification is silent in regard to which are the critical structural elements required in a polynucleotide to encode a PSST subunit of the NADH:ubiquinone oxidoreductase complex, nor there is any information as to which structural elements in the polynucleotide of SEQ ID NO: 9 are essential in a naturally occurring 80% structural homolog of the polynucleotide of SEQ ID NO: 9 such that the 80% structural homolog encodes a PSST subunit of the NADH:ubiquinone oxidoreductase complex.

While one could argue that the claimed genus of polynucleotides is adequately described since one could obtained polynucleotides of similar function by sequence comparison using the polynucleotide structures described in the specification and the prior art, the state of the art teaches that sequence comparison alone should not be used to determine function and that small structural changes can drastically change function. Bork (Genome Research, 10:398-400, 2000) teaches that protein function is context dependent, and both molecular and cellular aspects must be considered (page 398). Brenner (TIG 15:132-133, 1999) teaches the difficulty of accurately inferring function from homology and clearly states that most homologs must have different molecular and cellular functions (column 2, second paragraph, page 132). In regard to examples showing how small structural changes affect function,

Witkowski et al. (Biochemistry 38:11643-11650, 1999) teaches that one amino acid substitution transforms a β-ketoacyl synthase into a malonyl decarboxylase and completely eliminates β-ketoacyl synthase activity. Van de Loo et al. (Proc. Natl. Acad. Sci. 92:6743-6747, 1995) teaches that polypeptides of approximately 67% homology to a desaturase from *Arabidopsis* were found to be hydroxylases once tested for activity. Seffernick et al. teaches that two naturally occurring Pseudomonas enzymes having 98% amino acid sequence identity catalyze two different reactions: deamination and dehalogenation, therefore having different function. Broun et al. (Science 282:1315-1317, 1998) teaches that as few as four amino acid substitutions can convert an oleate 12-desaturase into a hydrolase and as few as six amino acid substitutions can transform a hydrolase to a desaturase. The art, as described above, clearly teaches that a genus of polynucleotides, as the one claimed, can potentially have many different functions which cannot be inferred by structural homology alone. The specification only discloses a single species of the genus which is insufficient to put one of ordinary skill in the art in possession of all attributes and features of all species within the claimed genus. Thus, one skilled in the art cannot reasonably conclude that Appellant had possession of the claimed invention at the time the instant application was filed.

Claim Rejections - 35 USC § 112 – Scope of Enablement

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

Claim 31 is rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for the polynucleotide of SEQ ID NO: 9, does not reasonably provide enablement for (1) a polynucleotide comprising a naturally occurring polynucleotide sequence at least 80% identical to the polynucleotide sequence of SEQ ID NO: 9 over the entire length of SEQ ID NO: 9, (2) a polynucleotide completely complementary to the polynucleotide of (1), or (3) an RNA equivalent of (1) or (2). The

specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims.

The criteria for undue experimentation, summarized in *In re Wands*, 8, USPQ2nd 1400 (Fed. Cir. 1988) are: 1) quantity of experimentation necessary, 2) the amount of direction or guidance presented, 3) the presence and absence of working examples, 4) the nature of the invention, 5) the state of prior art, 6) the relative skill of those in the art, 7) the predictability or unpredictability of the art, and 8) the breath of the claims.

The scope of the claims encompasses any polynucleotide of any function comprising a naturally occurring sequence 80% identical to the polynucleotide sequence of SEQ ID NO: 9 over the entire length of SEQ ID NO: 9. While the structure of the polynucleotide of SEQ ID NO: 9 is disclosed and a function has been asserted for the polypeptide encoded by the polynucleotide of SEQ ID NO: 9 (i.e. the polypeptide of SEQ ID NO: 1), the specification fails to disclose (1) other functions for all polynucleotides comprising a naturally occurring sequence 80% identical to the polynucleotide sequence of SEQ ID NO: 9 over the entire length of SEQ ID NO: 9, (2) which are the critical structural elements required in any polynucleotide to encode a PSST subunit of the NADH:ubiquinone oxidoreductase complex (i.e. only function disclosed), (3) which structural elements in the polynucleotide of SEQ ID NO: 9 are essential in a naturally occurring 80% structural homolog of the polynucleotide of SEQ ID NO: 9 such that the 80% structural homolog encodes a PSST subunit of the NADH:ubiquinone oxidoreductase complex, and (4) examples of other polynucleotides as encompassed by the claim with the exception of the polynucleotide of SEQ ID NO: 9.

The argument can be made that the claimed invention, i.e. polynucleotides of any function comprising a naturally occurring sequence at least 80% identical to the polynucleotide sequence of SEQ ID NO: 9 over the entire length of SEQ ID NO: 9, is enabled by the teachings of the specification and what is known in the prior art since one could obtained polynucleotides encoding polypeptides of similar

function to that of the polypeptide of SEQ ID NO: 1 by sequence comparison using the structures disclosed in the specification and those of the prior art. However, as previously discussed, the state of the art teaches the unpredictability of properly assigning function based solely on structural homology. As discussed above, Bork teaches that protein function is context dependent, and both molecular and cellular aspects must be considered (page 398). In addition, Brenner (TIG 15:132-133, 1999) teaches the difficulty of accurately inferring function from homology and clearly states that most homologs must have different molecular and cellular functions (column 2, second paragraph, page 132). Furthermore, the art clearly teaches examples in support of the teachings of Bork and Brenner, which show how small structural changes result in changes in function, therefore indicating that structural homologs may not share a similar function. Witkowski et al. teaches that one amino acid substitution transforms a β-ketoacyl synthase into a malonyl decarboxylase and completely eliminates β-ketoacyl synthase activity. Van de Loo et al. teaches that polypeptides of approximately 67% homology to a desaturase from *Arabidopsis* were found to be hydroxylases once tested for activity. Seffernick et al. teaches that two naturally occurring Pseudomonas enzymes having 98% amino acid sequence identity catalyze two different reactions: deamination and dehalogenation, therefore having different function. Broun et al. teaches that as few as four amino acid substitutions can convert an oleate 12-desaturase into a hydrolase and as few as six amino acid substitutions can transform a hydrolase to a desaturase. The art, as described above, clearly teaches that even one amino acid substitution can result in a polypeptide having different function, therefore the claimed polynucleotides can potentially encode proteins of many different functions which cannot be inferred by structural homology alone.

Therefore, due to the lack of relevant examples, the amount of information provided, the lack of knowledge about the critical structural elements required in a polynucleotide to encode a PSST subunit of the NADH:ubiquinone oxidoreductase complex, the lack of knowledge as to the structural elements in the polynucleotide of SEQ ID NO: 9 which are required in any naturally occurring 80% structural homolog

of the polynucleotide of SEQ ID NO: 9 to encode a PSST subunit of the NADH:ubiquinone oxidoreductase complex, and the unpredictability of the art in regard to assigning function based on structural homology, one of skill in the art would have to go through the burden of undue experimentation in order to (1) determine the functions of all the polypeptides encoded by the polynucleotides encompassed by the claim, (2) determine how to use those polynucleotides of unknown function, and (3) screen and isolate the potentially large number of polynucleotides encompassed by the claims to determine which ones encode PSST subunits of the NADH:ubiquinone oxidoreductase complex. Thus, Appellants have not provided sufficient guidance to enable one of ordinary skill in the art to make and/or use the invention as claimed.

(11) Response to Argument

Issue One: Rejection of claim 31 under 35 USC § 112, first paragraph, written description

On page 4, first paragraph of the Brief, Appellants submit that function is not required to describe and use the claimed polynucleotides. In addition, Appellants indicate that the Examiner has not provided evidence or scientific reasoning to support the allegation of lack of written description. Appellants refer to *Vas-cath, Inc. v. Mahurkar*, 19 USPQ2d 1111, 1117 (Fed. Cir. 1991) and the PTO's "Guidelines for Examination of Patent Applications Under the 35 U.S.C. Sec. 112, para. 1", published January 5, 2001, in support of the argument that the written description standard is fulfilled by both what is specifically disclosed and what is conventional or well known to one of skill in the art. Appellants submit that SEQ ID NO:1 and SEQ ID NO:9 are specifically disclosed in the application as well as variants of SEQ ID NO:1 and SEQ ID NO:9. According to Appellants, chemical and structural features of MITP-I (the polypeptide of SEQ ID NO: 1) are described in Table 2 and submit that one of ordinary skill in the art would recognize naturally-occurring variants of SEQ ID NO:9 at least 80% identical to SEQ ID NO:9. In addition, Appellants indicate that the specification describes how to determine whether a given

sequence falls within the "at least 80% identical" scope. It is Appellant's opinion that there is no requirement that the claims recite particular polynucleotide variant sequences because the claims already provide sufficient structural definition of the claimed subject matter. Because the recited polynucleotide variants are defined in terms of SEQ ID NO: 9, it is Appellant's position that the precise chemical structure of every polynucleotide variant within the scope of the claims can be discerned. Appellant's conclude that the Examiner's position is nothing more than a misguided attempt to require Appellants to unduly limit the scope of their claimed invention.

While the Examiner acknowledges (1) *Vas-cath, Inc. v. Mahurkar* and the PTO's "Guidelines for Examination of Patent Applications Under the 35 U.S.C. Sec. 112, para. 1", published January 5, 2001, (2) the disclosure of the structure of the polynucleotide of SEQ ID NO: 9 and the corresponding polypeptide (SEQ ID NO: 1, MITP-1), (3) the disclosure of the closest structural homolog in Table 2, first entry, and (4) algorithms known in the art for sequence alignment and calculation of % homology/identity as described in Table 5 of the specification, the Examiner disagrees with Appellant's contention that (1) function is not required to describe and use the claimed polynucleotides, (2) the specification teaches how to recognize naturally-occurring variants of the polynucleotide of SEQ ID NO: 9 as recited in the claim, or (3) the Examiner has not presented evidence to show that the claimed genus is not adequately described. As indicated in previous Office Actions and reiterated herein, while it is agreed that the claim defines the genus of polynucleotides claimed by its structure, it encompasses polynucleotides encoding polypeptides of <u>any</u> function. In view of the fact that the specification discloses only one function (i.e. PSST subunit of the NADH:ubiquinone oxidoreductase complex) for only one of the species in the genus (i.e. the polynucleotide of SEQ ID NO: 9 and its corresponding polypeptide), and taking into consideration the teachings of Bork, Broun et al., Brenner (TIG 15:132-133, 1999) , Van de Loo et al., Seffernick et al., and Witkowski et al. already discussed in Paper No. 9 (Non Final Rejection), 13 (Final Rejection) and 17 (Advisory Action), it would be clear to one of ordinary skill

in the art that the genus claimed is not adequately described since it almost certainly encompasses polynucleotides encoding polypeptides of variable function which are not disclosed by the specification. The genus of polynucleotides claimed is one of substantial variation in function. The claimed genus clearly encompasses some species which encode PSST subunits of the NADH:ubiquinone oxidoreductase complex but yet also encompasses many more species which encode polypeptides lacking such function. It is well established in the art that many single amino acid substitutions in the amino acid sequence of an enzyme will result in loss of activity. As one adds additional changes, the number of possible structural homologs which have 80% identity to SEQ ID NO: 9 is enormous ($> 10^{20}$). Only a very minute fraction of these structural homologs will encode PSST subunits of the NADH:ubiquinone oxidoreductase complex, or will occur naturally. Applicants claim all those species which occur naturally. However, there is no means for a skilled artisan to know which of the enormous number of polynucleotides having at least 80% sequence identity to the polynucleotide of SEQ ID NO: 9 are within the naturally occurring genus claimed. Furthermore, the claimed genus will encompass polynucleotides encoding both functional and non-functional PSST subunits of the NADH:ubiquinone oxidoreductase complex, and may even encompass species which do not encode PSST subunits of the NADH:ubiquinone oxidoreductase complex, but encode polypeptides having a different undisclosed function. As such, the species within the genus are highly variable in functional features. In addition, while the specification teaches how one can calculate % identity as recited in the claim, the specification does not provide any teaching as to how to recognize naturally occurring variants of the polynucleotide of SEQ ID NO: 9 as encompassed by the claim. Therefore, it is unclear as to how one of skill in the art can reasonably conclude that the claimed genus of polynucleotides is adequately described if it is a genus of substantial variation in function and only one structure associated with that function has been disclosed.

A. The present claim allegedly defines the claimed genus through the recitation of chemical structure

On page 5 of the Brief, and continuing on pages 6 and 7, Appellants argue that court cases in which DNA claims have been at issue commonly emphasize that the recitation of structural features or chemical or physical properties are important factors to consider in a written description analysis of such claims. Appellants refer to the decisions in *Fiers v. Revel*, 25 USPQ2d 1601, 1606 (Fed. Cir. 1993) and *University of California v. Eli Lilly and Co.*, 43 USPQ2d 1398, 1406 (Fed. Cir. 1997) in support of the argument that, in contrast to the issues in *Fiers* and *Lilly*, the instant claim recites a chemical structure and is fundamentally different from those found invalid in *Fiers* and *Lilly*.

While the Examiner agrees that the claimed polynucleotides must share a common structural feature, i.e. at least 80% sequence identity to the polynucleotide of SEQ ID NO: 9 over the entire length of SEQ ID NO: 9, and acknowledges the findings in *Fiers v. Revel* and *Univ. of California v. Eli Lily and Co.*, it is noted that claimed genus is one of substantial variation in function. Variation in functional features was not an issue in *Fiers* or *Lilly* because in those cases the disputed claims recited a functional limitation. In the instant case, there is no functional limitation. As indicated above, the written description requirement for a claimed genus may be satisfied through sufficient description of a representative number of species sufficient to show applicants were in possession of the claimed genus. A representative number of species means that the species that are adequately described are representative of the entire genus. In the instant case, one cannot reasonably conclude that the single species disclosed, i.e. SEQ ID NO: 9, is representative of the claimed genus in view of the fact that the claimed polynucleotides can potentially have many functions which are undisclosed. In view of the teachings of Bork, Broun et al., Brenner (TIG 15:132-133, 1999) , Van de Loo et al., Seffernick et al. and Witkowski et al., one of skill in the art would recognize that the claimed invention belongs to an unpredictable art which cannot be adequately described by disclosing a single species. Therefore, one cannot reasonably conclude that the polynucleotide of SEQ ID NO: 9 is sufficient to adequately described all features and

attributes of polynucleotides comprising a naturally occurring sequence which is at least 80% identical to that of SEQ ID NO: 9 over the entire length of SEQ ID NO: 9.

B. The present claim allegedly defines a genus which is not large and variable

On page 7 of the Brief, last paragraph, and continuing on page 8, Appellants submit that the claimed genus is not large and variable as asserted by the Examiner. Appellants refer to the teachings of Brenner et al. (Proc. Natl. Acad. Sci. USA 95:6073-6078, 1998) and state that the instant reference discloses that 30% identity is a reliable threshold for establishing evolutionary homology between two sequences aligned over at least 150 residues and that 40% or more identity over at least 70 residues is reliable in signifying homology between proteins. As such, it is Appellant's conclusion that, in accordance with Brenner et al., naturally occurring polynucleotides may exist which could be characterized as PSST subunits of the NADH:ubiquinone oxidoreductase complex with as little as 40% identity over at least 70 residues of the polypeptide of SEQ ID NO: 1. Appellants submit that the claimed genus of polynucleotides is not highly variable since the recitation of "at least 80% identical" encompasses less variation than that of "40% identity over at least 70 residues of the polypeptide of SEQ ID NO: 1". Appellants further refer to the teachings of Bork, Van de Loo et al., Seffernick et al., Broun et al., Brenner (TIG 15:132-133, 1999) and Witkowski et al., and indicate that while these references may show that functional predictions cannot be made with 100% accuracy, they demonstrate that a skill artisan would believe that such predictions would be reasonably accurate. Furthermore, Appellants argue that Brenner et al. (Proc. Natl. Acad. Sci. USA 95:6073-6078, 1998) provides reasonable guidelines for judging homology and that all that is required to satisfy the written description requirement of 35 USC § 112, first paragraph is that one of skill in the art would reasonably understand that Appellants were in possession of the claimed invention at the time of filing.

While the Examiner agrees that the scope of a genus of polynucleotides comprising a naturally occurring sequence at least 80% identical to that of SEQ ID NO: 9 over the entire length of SEQ ID NO: 9 is smaller than that of a genus of polynucleotides encoding polypeptides having at least 40% sequence identity over at least 70 residues of the polypeptide of SEQ ID NO: 1, the Examiner disagrees with Appellant's contention that the claimed genus of polynucleotides is not a genus of substantial variation in function. As indicated by the teachings of Bork, Van de Loo et al., Seffernick et al., Broun et al., Brenner (TIG 15:132-133, 1999) and Witkowski et al., even highly homologous structural homologs (1-6 amino acid mismatches) did not share the same function. Therefore, in the absence of any evidence indicating (1) the degree of structural variability among all PSST subunits of the NADH:ubiquinone oxidoreductase complex, (2) which are the structural elements which are essential for polypeptides to be PSST subunits of the NADH:ubiquinone oxidoreductase complex, or (3) which are the 3D conformations in a protein which are indicative of this function, it is unclear as to how one of skill in the art can reasonably conclude that the claimed polynucleotides do not have the potentiality of encoding polypeptides of diverse function.

In regard to the teachings of Brenner et al. (Proc. Natl. Acad. Sci. USA 95:6073-6078, 1998), it is noted that the purpose of the study of Brenner et al. was to identify distant evolutionary structural homology using sequence comparison algorithms. Brenner et al. does not teach that the results obtained can be extrapolated for use in predicting functional homology of any unknown protein. Furthermore, Brenner et al. clearly states that their comparisons "have been assessed using proteins whose relationships are known reliably from their structures and functions, as described in the SCOP database" (page 6073, Abstract). The proteins within the SCOP database have been fully characterized, meaning their functions have been characterized by empirical laboratory experiments and their 3D structures have been generated. Therefore, the results disclosed in Brenner et al. are applicable only for identifying evolutionary structural homology and not functional homology, as Appellants assert. Even if one assumes that the results of

Brenner et al. could be applied for functional annotation of uncharacterized proteins of any function, Brenner et al. teaches that the 30% identity for alignments of at least 150 residues threshold is applicable only to the protein database used (PDB90D-B) and that the 40% identity over at least 70 residues threshold is a reasonable threshold for a database of the size and composition of that of PDB90D-B. See page 6076, right column, lines 20-26. As indicated in the Advisory Action and reiterated herein, nowhere in the instant reference, is there a statement indicating that these thresholds can be used to predict the function of any unknown protein. Therefore, in view of the teachings of the art as presented by the Examiner, as well as Appellants, it is unclear as to how one of skill in the art can reliably predict the function of any polypeptide with a 30% sequence identity over 150 residues or 40% identity over 70 residues threshold based solely on sequence homology as asserted by Appellants. Thus, one cannot reasonably conclude that a genus of polynucleotides comprising naturally occurring sequences at least 80% identical to the sequence of SEQ ID NO: 9 over the entire length of SEQ ID NO: 9, is not a genus which is functionally variable.

In addition to the arguments addressed above, it is important to note that the protein comparisons disclosed by Brenner et al. are most likely carried out among proteins corresponding to the most common allele of particular loci. As known in the art, almost all human genes would have several alleles which can be either functional (most common) and non-functional (usually rare). However, Brenner et al. most likely does not include those proteins corresponding to less frequently found functional alleles or non-functional alleles. Since the study by Brenner et al. most likely excludes proteins corresponding to less frequently found alleles or non-functional alleles, and in view of the fact that this reference does not teach that one could use their results in the accurate functional annotation of any protein based solely on structural homology, as discussed above, it is unclear as to how one of skill in the art can reasonably conclude that the teachings of Brenner et al. can be evidence to support the argument that the only species disclosed (i.e. the polynucleotide of SEQ ID NO: 9) is representative of a genus of polynucleotides which

encompass functional and non-functional (potentially disease causing) alleles of the gene of SEQ ID NO: 9 as well as functional and non-functional alleles of genes which share structural homology to the gene of SEQ ID NO: 9 but are associated with a completely different biological function.

On page 9 of the Brief, second paragraph and continuing on page 10, first paragraph, Appellants submit that the SCOP database as discussed in Brenner et al. (Proc. Natl. Acad. Sci. USA 1998, 95:6073-6078) is a protein database with known structures and that there is no information in the paper about different loci. Appellants further indicate that the instant reference does not discuss predicting functional similarity but rather evolutionary relationships. Appellants further state that one cannot test the ability of a sequence comparison method in predicting structural homology if one starts with protein sequences whose structures were not already known previously and independently of the sequence comparison. Appellants indicate that the SCOP database is a test set and that the relationships among the SCOP proteins are already known and that the results described by the instant reference allow one to generalize to the much more common situation of not knowing the structural and functional relationships between two polypeptide sequences and trying to use sequence comparison methods to predict those relationships.

As indicated in the Advisory Action (page 7, paragraph 11), the Examiner is aware of the fact that the SCOP database comprises proteins for which three dimensional (3D) structures and functions are well known and characterized. Furthermore, it is noted that the Examiner is also aware of the fact that (1) the objective of the study described in the instant reference is to assess sequence comparison algorithms to determine distant evolutionary homology using reliable structurally identified evolutionary relationships, and (2) one cannot test the ability of a sequence comparison method in predicting structural homology if one starts with protein sequences which have not been validated independently. In regard to Appellant's contention that the instant reference does not refer to different loci, it is noted that while the instant reference does not refer specifically to different loci, it is assumed that different loci are involved

since the polypeptides in the SCOP databases, while evolutionarily related, may not be of identical function and may be encoded by different genes.

On page 10 of the Brief and continuing on page 11, Appellants submit that function is immaterial to the written description requirement given what is disclosed in the specification and what is known in the art. According to Appellants, (1) it is routine to calculate % identity, (2) it is routine to use naturally-occurring polynucleotides in toxicology testing, and (3) function is not required in toxicology testing. Appellants further submit that the rules described by Brenner et al. (Proc. Natl. Acad. Sci. USA 95:6073-6078, 1998) are ideal for addressing the 3D-primary amino acid sequence relationship. According to Appellants, the SCOP database can be used to derive general rules for identifying homology between proteins which have not been fully characterized. It is Appellant's contention that if it were necessary to have a fully characterized protein before it was analyzed using the standards of Brenner et al., then there would be no need for such analysis because the protein would already have been characterized. It is Appellant's conclusion that there is no need for an actual determination of 3D structure to use the general rules of Brenner et al. and that a 3D structure is not required to ascertain its function due to the fact that many there are many proteins with known function for which there is no 3D structure determined yet.

While the Examiner agrees that (1) it is routine to calculate % identity, (2) many polynucleotides have been used in toxicology testing, and (3) the 3D structure of many proteins of known function has not been determined yet, the Examiner disagrees with Appellant's contention that function is irrelevant. First, it is noted that arguments in regard to function as they relate to a specific use, i.e. toxicology testing, are more appropriate in regard to enablement. As such, they will be addressed in response to arguments related to enablement. However, contrary to Appellant's statements, functional features are not irrelevant to a written description inquiry. Function is in fact highly relevant to a sufficient description of a compound as it is relevant to its use(s). Compounds which have different functional features, as are those encompassed by the claimed genus, cannot be used in the same manner. Thus a single species is not

representative of all species claimed. As indicated in previous Office Actions, above, and reiterated herein, the written description requirement requires sufficient description of a representative number of species sufficient to show possession of the claimed genus. In the instant case, one cannot reasonably conclude that the single species disclosed, i.e. SEQ ID NO: 9, is representative of the claimed genus in view of the fact that the claimed polynucleotides can potentially have many functions which are undisclosed. In view of the teachings of Bork, Broun et al., Brenner (TIG 15:132-133, 1999), Van de Loo et al., Seffernick et al. and Witkowski et al., one of skill in the art would recognize that the claimed invention belongs to an unpredictable art which cannot be adequately described by disclosing a single species.

In regard to the teachings of Brenner et al. (Proc. Natl. Acad. Sci. USA 95:6073-6078, 1998) and the disclosure of 3D structures as it relates to the polypeptide of the instant application, it is noted that it is not the Examiner's contention that the 3D structure of the polypeptide of SEQ ID NO: 1 is required to adequately described the genus of polynucleotides claimed. Instead, as indicated in the Advisory Action (page 7) and reiterated herein, there is no 3D structural analysis of PSST subunits of the NADH:ubiquinone oxidoreductase complex which would support Appellant's assertion that naturally occurring polypeptides having as little as 40% sequence identity over 70 residues of the polypeptide of SEQ ID NO: 1 can be characterized as PSST subunits of the NADH:ubiquinone oxidoreductase complex. In fact, this is clearly untrue. The existence of naturally occurring single substitution mutations which result in a loss of enzymatic function are well known, and many important genetic diseases are the result of such alleles. Such non-functional alleles clearly have much higher sequence homology to their corresponding active alleles than 40% or 80%, but they do not share the active allele's function. As discussed above, the thresholds described by Brenner et al. were clearly determined using databases where 3D structures and functions were known. Therefore, as evidenced by the art, the genus of polynucleotides claimed can have substantial functional variability. Appellant's arguments in regard to

the rules described by Brenner et al. (Proc. Natl. Acad. Sci. USA 95:6073-6078, 1998) are not deemed persuasive in view of the fact that they do not in any way contradict the evidence already presented by the Examiner in regard to the potential functional variability of the claimed genus, as already discussed above. As such, in view of the variability of the genus, one cannot reasonably conclude that a single species is sufficient to describe the claimed genus.

On page 11 of the Brief and continuing on page 12, Appellants submit that it is well known in the art that sequence similarity is predictive of similarity in functional activity. Appellants further submit that Hegyi et al. (J. Mol. Biol. 288:147-164, 1999) teaches that there is a low chance that a single-domain protein, highly homologous to a known enzyme has a different function. In addition, Appellants argue that Hegyi et al. (Genome Research 11: 1632-1640, 2001) conclude that "the probability that two single-domain proteins that have the same superfamily structure have the same function (whether enzymatic or not) is about 2/3" and that, for multi-domain proteins with "almost complete coverage with exactly the same type and number of superfamilies, following each other in the same order" "the probability that the functions are the same in this case was 91%.". Furthermore, Appellants argue that Hegyi et al. (Genome Research 11: 1632-1640, 2001) teaches that Wilson et al. (2000) found that function is not conserved below 30-40% identity, although the broad functional class is usually preserved for sequence identities as low as 20-25%, given that the sequences have the same fold and confirmed the previously established general exponential relationship between structure and sequence similarity. Therefore, Appellants conclude that it is well known in the art that sequence identity can be used to reliably predict functional similarity.

For the record, it is noted that this is the first time the Examiner has been presented with the references by Hegyi et al. (J. Mol. Biol. 288:147-164, 1999) and Hegyi et al. (Genome Research 11: 1632-1640, 2001). While the Examiner acknowledges the teachings of Hegyi et al. (J. Mol. Biol. 288:147-164, 1999) and Hegyi et al. (Genome Research 11: 1632-1640, 2001), the Examiner disagrees

with Appellant's contention that it is well known that sequence identity can be used to reliably predict functional similarity. Neither one of the new references presented by Appellants in the Brief contradict in any way the fact that the state of the art in regard to accurate annotation of function based on structural homology is still unpredictable and while there are instances where accurate functional annotations have been made, as indicated by Hegyi et al. (Genome Research 11: 1632-1640, 2001), even among single domain proteins sharing the same structural superfamily there is only a 67% certainty in accurately predicting function and only 35% certainty for multi-domain proteins which share a single structural superfamily (Abstract, page 1632). According to Hegyi et al. (Genome Research 11: 1632-1640, 2001; Abstract), multi-domain proteins, which are the bulk of ORFs (open reading frame) in eukaryotic genomes, have less functional conservation except when the share the same combination of domain folds (3D). Therefore, in view of the teachings of Bork, Broun et al., Brenner, Van de Loo et al., Seffernick et al. and Witkowski et al. presented by the Examiner, as well as the teachings of Hegyi et al. (Genome Research 11: 1632-1640, 2001), it is clear that sequence identity can not be used to reliably predict functional similarity in every case.

In regard to the teachings of Hegyi et al. (J. Mol. Biol. 288:147-164, 1999), it is noted that the "low chance of a structural homolog to have a different function" statement refers to single domain enzymes which are highly homologous and not to just any class of proteins. Furthermore, neither the specification nor the art teaches (1) the level of structural homology required for one to conclude that polynucleotides having at least 80% sequence identity to the polynucleotide of SEQ ID NO: 9 over the entire length of SEQ ID NO: 9 would most likely encode PSST subunits of the NADH:ubiquinone oxidoreductase complex, or (2) what constitutes "highly homologous" as it refers to PSST subunits of the NADH:ubiquinone oxidoreductase complex. In addition, the art, as evidenced by Witkowski et al., Seffernick et al. and Broun et al., teaches that even for enzymes, small amino acid changes ranging from

1-6 amino acids resulted in major changes in function. Therefore, even highly structurally homologous enzymes did not share the same function.

As discussed above in regard to Brenner et al., it is also noted that neither Hegyi et al. (Genome Research 11: 1632-1640, 2001) nor Hegyi et al. (J. Mol. Biol. 288:147-164, 1999) appear to include proteins corresponding to less frequently found alleles or non-functional alleles in their studies. Since the results disclosed by the instant references are most likely representative of those proteins corresponding to the most common alleles of specific loci, and none of the instant references provide any teaching or suggestion as to the accurate functional annotation of any protein based solely on structural homology, one of skill in the art cannot reasonably conclude that the art presented by Appellants can be considered evidence to show that the disclosure of a single species (i.e. the polynucleotide of SEQ ID NO: 9) is sufficient to adequately describe a genus of polynucleotides which encompass functional and non-functional (potentially disease causing) alleles of the gene of SEQ ID NO: 9 as well as functional and non-functional alleles of genes which share structural homology to that of SEQ ID NO: 9 but are associated with a totally different biological function.

C. The references cited by the Examiner are allegedly not relevant to the instant claim

On page 12 of the Brief, second paragraph and continuing on pages 13-15, Appellants argue that the references cited by the Examiner are not relevant to the instant claim. Appellants cite a recent Federal Circuit decision in *Boehringer Ingelheim Vetmedica, Inc. v. Schering Plough Corporation*, 65 USPQ2d 1961 (CA FC 2003) and assert that the Examiner appears not to differentiate between the finding that a single amino acid substitution may alter the function of a polypeptide and the opinion of one of skill in the art that, more likely than not, a single amino acid substitution or up to 20% amino acid substitutions or up to 20% nucleotide substitutions will alter the function of a polypeptide. Appellants submit that the Examiner has not provided any evidence that polypeptides encoded by the genus of polynucleotides

claimed would not be predicted to have the same function as that of SEQ ID NO: 1. Furthermore, Appellants reiterate that function is immaterial to the written description requirement in view of the disclosure and what is known to one of skill in the art. Appellants assert that the teachings of Bork support the use of sequence comparison for predicting function. Furthermore, Appellants assert that the fatty acyl hydroxylases and fatty acyl desaturases of Van de Loo et al. catalyze a similar reaction and that the reaction mechanisms of both enzymes are similar based on sequence homology. In regard to Broun et al., Appellants argue that since the enzymatic functions described in Van de Loo et al. and Broun et al. are similar, it is not surprising that they share 67% sequence homology. Accordingly, Appellants submit that the instant references are not relevant since Appellants have not asserted that the claimed polynucleotides encode a fatty acyl hydroxylase or a fatty acyl desaturase. In regard to Seffernick et al., Appellants argue that the two enzymes described belong to a class of bacterial amidohydrolases and therefore, they do not have a diverse function as asserted by the Examiner. Moreover, Appellants argue that since they have not asserted that the claimed polynucleotides encode bacterial aminohydrolases, this reference is irrelevant. Appellants argue that nowhere does Brenner (TIG 15:132-133, 1999) teach that all functional annotation yields incorrect results or that one of skill in the art would not find it more likely than not that the claimed polynucleotide variants at least 80% sequence identical to SEQ ID NO: 9 would encode polypeptides with the same biological function as that of the polypeptide of SEQ ID NO: 1. Appellants submit that the Examiner appears to ignore the fact that Witkowski et al. teaches that both the wild type and the Cys161Gln mutant enzyme can carry out the malonyl decarboxylase reaction and that Witkowski et al. made mutations of a critical amino acid and that an example of an artificially created mutant would not lead one of skill in the art to doubt that the claimed polynucleotides would encode polypeptides having the same biological function as that of the polypeptide of SEQ ID NO: 1. Appellants conclude that a statement in the Witkowski et al. reference in regard to β–ketoacyl synthases sharing extensive similarity and a common reaction mechanism is evidence that one of skill in the art would reasonably conclude that

the claimed variants would encode polypeptides having the same function as that of the polypeptide of SEQ ID NO: 1.

In regard to the recent decision in *Boehringer Ingelheim Vetmedica, Inc. v. Schering Plough Corporation*, 65 USPQ2d 1961 (CA FC 2003), it is noted that the issue being discussed in the instant rejection is not equivalence, which is the issue which was discussed in *Boehringer Ingelheim Vetmedica, Inc. v. Schering Plough Corporation*. In fact, the statement quoted by Applicants further supports the Examiner's argument that even a single amino acid substitution may drastically alter the function of a gene or a protein. It is noted that the Examiner is not contending that almost all of the species in the claimed genus of polynucleotides will encode proteins of different functions. Instead, contrary to Appellant's assertion, the Examiner has presented evidence to show that the claimed genus of polynucleotides have the potential of encoding proteins of different functions and that those functions have not been disclosed by the specification. Furthermore, it is noted that the claimed genus will undoubtedly encompass at least species which will encode PSST subunits of the NADH:ubiquinone oxidoreductase complex and species that will encode inactive PSST subunits of the NADH:ubiquinone oxidoreductase complex. These species would have a different function and use. In view of the evidence presented, the genus of polynucleotides claimed can be substantially variable in function and a single disclosed species is not deemed sufficient to meet the written description requirements under 35 USC § 112, first paragraph.

In regard to the teachings of Bork, it is not the Examiner's contention that sequence homology is completely unreliable and that it should never be used to make functional predictions but rather the unpredictability of solely using sequence homology to accurately determine function. As indicated by Bork, while accurate predictions have been made in some cases, Bork also teaches that while gene annotation using structural homology is routine, the error rate is considerable (page 399, second column)

as evidenced in Table 1 and that the numbers in Table 1 are overestimates (page 400, first column, last paragraph).

In regard to the irrelevance of Van de Loo et al. (Proc. Natl. Acad. Sci. 92:6743-6747, 1995), Broun et al. (Science 282:1315-1317, 1998) and Seffernick et al. (J. Bacteriol. 183(8):2405-2410, 2001), it is noted that even if the enzymes described in those references belong to the same general class of enzymes, they are not the same since they catalyze different reactions and/or have different substrates. A description of function with specificity is necessary for one to know how to use a compound. Thus merely describing a general class into which the enzymes in the instant references could fall would not be sufficient to describe their specific function and substrate. Furthermore, the relevance of these references is not in regard to whether the polynucleotides claimed encode fatty acyl hydroxylases, desaturases or bacterial amidohydrolases but rather to present state of the art evidence establishing the unpredictability of assigning any specific function based on sequence homology in the absence of any information as to how structure correlates with the only function disclosed, i.e. PSST subunit of the NADH:ubiquinone oxidoreductase. Similarly, it is not the Examiner's contention that the Brenner (TIG 15:132-133, 1999) reference teaches that all functional annotations yield incorrect results or that one of skill in the art would find it more likely than not that the claimed polynucleotides would encode proteins having the same function as that of the polypeptide of SEQ ID NO: 1. Instead, the Brenner (TIG 15:132-133, 1999) reference was presented as evidence to indicate the general consensus in the art in regard to the unpredictability of accurate annotation of function, and particularly function specific enough to provide a use for a gene, based on structural homology and how one cannot assume that structural homologs, such as those claimed, will encode proteins of the same function without some additional information providing a correlation between structure and function.

In regard to Witkowski et al., it is noted that this reference was also presented as supporting evidence in regard to the potential functional variability of the genus claimed. While it is agreed that (1)

Witkowski et al. states that both the wild type and the Cys161Gln mutant enzyme can carry out the malonyl decarboxylase reaction, (2) Witkowski et al. made mutations of a critical amino acid, (3) Witkowski et al. states that β–ketoacyl synthases share extensive similarity and a common reaction mechanism, it is noted that these facts do not alter the fact that even a single amino acid substitution can result in functional changes, which would change the specific uses of the corresponding polynucleotide/genes. As indicated by Witkowski et al. (Abstract), the mutant enzyme is not capable of carrying out the condensation reaction (i.e. complete inhibition) whereas the decarboxylation reaction rate increases by 2 orders of magnitude. While both the wild type and the mutant enzyme can carry out the decarboxylation reaction, it is noted that the levels of decarboxylating enzymatic activity are very different in both proteins. Furthermore, while the mutation was made in a critical amino acid residue, it is noted that the claim does not have a limitation in regard to which nucleotides are excluded from the 20% variation encompassed by the claim, i.e. nucleotides encoding critical amino acids are also included, and the specification provides no information as to which are the critical amino acid residues in the polypeptide of SEQ ID NO: 1 related to function. In regard to the statement in Witkowski et al. related to the extensive similarity and common reaction mechanism of β–ketoacyl synthases, it is noted that (1) neither the specification nor the art disclose any functional correlation between PSST subunits of the NADH:ubiquinone oxidoreductase complex and β–ketoacyl synthases which would lead one of skill in the art to conclude that the statement regarding β–ketoacyl synthases is applicable to PSST subunits of the NADH:ubiquinone oxidoreductase complex, and (2) neither the specification nor the art provide any information as to the level of structural variability found among all PSST subunits of the NADH:ubiquinone oxidoreductase complex.. Thus, is it unclear as to how the level of similarity and common reaction mechanism of β–ketoacyl synthases is in any way evidence that the claimed polynucleotide variants would encode PSST subunits of the NADH:ubiquinone oxidoreductase complex, as asserted by Appellants.

D. The state of the art at the time of the present invention does not obviate an adequate written description of the claimed invention.

On page 15 of the Brief and continuing on page 16, Appellants argue that the state of the art at the time of the present invention is further advanced than at the time of the *Lilly* and *Fiers* applications. Applicants argue that the state of the art was at essentially the dark ages of recombinant DNA technology when the *Lilly* and *Fiers* applications were filed, whereas the instant application was filed 19 years after, when much has happened in the development of recombinant DNA technology.

While it is agreed that much has happened in the area of recombinant DNA technology since 1977, the state of the art after 1999 as extensively discussed above, teaches the unpredictability of determining function based on structural homology without any teaching or suggestion as to how structure correlates with function.

E. Summary

In page 16 of the Brief, second paragraph, Appellants submit that the Final Action failed to base its written description analysis on whatever is now claimed and that the Action did not provide an appropriate analysis taking into consideration cases such as *Lilly* and *Fiers*. In particular, Appellants refer to the importance of structural features in the written description analysis. Appellants reiterate that the claimed polynucleotides are adequately describe in view of the Brenner et al. (Proc. Natl. Acad. Sci. USA 95:6073-6078, 1998) paper and that the advances in the state of the art since the *Lilly* and *Fiers* cases were not given consideration in the Final Office or the Advisory Action.

In regard to arguments as they relate to *Lilly* and *Fiers*, these arguments have been fully addressed under section A above. In regard to the teachings of Brenner et al. (Proc. Natl. Acad. Sci.

USA 95:6073-6078, 1998), these arguments have been fully addressed under section B above. In regard to Appellant's contention that the Examiner did not give consideration to arguments related to advances in the state of the art since the *Lilly* and *Fiers* cases, it is noted that these arguments were considered and addressed in the Advisory Action on page 10, paragraph 14 and are also address herein under section D above.

Issue Two: Rejection of claim 31 under 35 USC § 112, first paragraph, enablement

A. How to make

On page 17 of the Brief, third paragraph and continuing on page 18, Appellants indicate that SEQ ID NO: 1 and 9 are specifically disclosed in the specification and that variants of the polynucleotide of SEQ ID NO: 9 and the polypeptide of SEQ ID NO: 9 are described in the specification. According to Appellants, the specification describes how to find naturally occurring analogs and homologs in other individuals and species as well as how to use CLUSTAL V and BLAST to determine whether a given polynucleotide falls within the "at least 80% sequence identity over the entire length of SEQ ID NO: 9" scope. Furthermore, Appellants submit that the making of the claimed polynucleotides is disclosed in the specification, therefore satisfying the "how to make" requirements of 35 USC § 112, first paragraph. Appellants refer to the Advisory Action and state that claim 31 is not limited to polynucleotides encoding PSST subunits of the NADH:ubiquinone oxidoreductase complex. Appellants also refer to the Advisory Action in regard to the Examiner's acknowledgement that making the structural homologs as recited in the claim is not undue experimentation.

While the Examiner agrees that (1) the specification discloses the structure of the polynucleotide of SEQ ID NO: 9 and the polypeptide of SEQ ID NO: 9, (2) CLUSTAL V and BLAST can be used to determine whether a given polynucleotide falls within the "at least 80% sequence identity over the entire length of SEQ ID NO: 9" scope, (3) making the claimed polynucleotides is not undue experimentation

since synthesis of polynucleotides is known in the art, and (4) the specification teaches the use of probes to detect variants of the polynucleotide of SEQ ID NO: 9, as indicated in the Advisory Action and reiterated herein, the specification fails to teach how to isolate and/or identify naturally-occurring polynucleotides as claimed, such as allelic variants of the polynucleotide of SEQ ID NO: 9, encoding PSST subunits of the NADH:ubiquinone oxidoreductase complex. While it is agreed that probes can be used to detect those polynucleotides which would hybridize to the probe, there is no teaching as to how to differentiate between those polynucleotides hybridizing to the probe which would encode proteins of any function and those polynucleotides detected with the probe which would encode PSST subunits of the NADH:ubiquinone oxidoreductase complex. As indicated above, there is no teaching or suggestion as to how the structure of the polynucleotide of SEQ ID NO: 9 relates to the structure of any naturally-occurring variant as claimed, and the art does not provide any indication of how a naturally-occurring variant is representative of unknown naturally-occurring variants. In the case of alleles, there is no indication in the art that would suggest that the structure of one provides guidance to the structure of others. In regard to arguments that making the claimed polynucleotides would not constitute undue experimentation, it is reiterated herein that while one of skill in the art would know how to make 80% sequence homologs of the polynucleotide of SEQ ID NO: 9, making and testing the extremely large number of polynucleotides encompassed by the claim and determining (1) the function of the polypeptides encoded by them, or (2) whether the polypeptides encoded by them are PSST subunits of the NADH:ubiquinone oxidoreductase complex, would constitute undue experimentation. Since a large amount of screening would be required in the instant case and the specification provides no guidance as to how the experimentation should proceed, one cannot reasonably conclude that the specification is enabling for the full scope of the claim.

B. How to use

On page 18 of the Brief, and continuing on pages 19-20, Appellants argue that the rejection of claim 31 is improper since the claim is enabled and has patentable utility. Appellants refer to several uses such as in toxicology testing, drug development, and disease diagnosis, which according to Appellants, do not require knowledge of function. Appellants further submit that as a result of these uses, the claimed invention already enjoys significant commercial success. In addition, Appellants refer to a declaration by Dr. Tod Bedilion, a consultant for Incyte Genomics, Inc., which is the assignee of record for the instant application. According to Appellants, the Bedilion declaration describes how the claimed polynucleotides can be used in gene expression monitoring applications and those applications useful in developing drugs and monitoring their activity. As such, it is Appellant's opinion that the Bedilion declaration demonstrate that one of skill in the art can achieve beneficial results from the claimed polynucleotides in the absence of any knowledge as to the precise function of the proteins encoded by them.

As indicated in the Advisory Action (page 2, paragraph 4; pages 12-14) and indicated by Appellants, the Bedilion Declaration was not considered by the Examiner for the following reasons. The declaration when first introduced was not properly executed since it has not been signed and dated. More importantly, however, the declaration, which was submitted in response to the Final Action, was not necessitated by new issues raised by the Examiner such that it would have been proper under 37 CFR 1.195. While Appellants alleged new issues raised by the Examiner in the Final Action as justification for the late submission of the Bedilion declaration, as indicated in the Advisory Action (page 13, paragraph 20), the record shows that it was Appellant and not the Examiner who introduce new arguments in regard to the use of the claimed invention, as evidenced by the references and arguments previously presented in Paper No. 12. The Examiner merely addressed the arguments and issues raised by Appellants. Appellants submitted arguments in Paper No. 12, filed on 6/12/2002 in regard to the many uses described

in the specification for the claimed polynucleotides such as in toxicology testing, drug development and diagnosis of disease, alleging that theses uses do not require knowledge of function. Furthermore, Appellants submitted references by Steiner et al. (Toxicology Letters 112-113:467-471, 2000), Rockett et al. (Xenobiotica 29:655-691, 1999), Nuwaysir et al. (Molecular Carcinogenesis 24:153-159, 1999), Rockett et al. (Environ. Health Perspec. 107:681-685, 1999) as evidence of the state of the art in regard to toxicology testing, its use in the pharmaceutical industry, and the genes/nucleic acids which are incorporated in toxicology testing. Appellants also submitted in Paper No. 12, an e-mail from Dr. Cynthia Afshari (NIH) to an Incyte Genomics employee (Diana Hamlet-Cox) to support the argument that any gene is relevant for screening of toxicological effects, and examples of Incyte collaborators or customers who have been able to obtain benefits from the information provided by Incyte's databases. Therefore, it was Appellant and not the Examiner who introduce new arguments in regard to the use of the claimed invention, as evidenced by the references and arguments previously presented in Paper No. 12.

While Appellants were aware that the Bedilion declaration would not be considered, as acknowledged by Appellants in the Brief, page 19, second paragraph, many of the arguments in the Brief refer to this declaration. In view of the fact that this declaration has not been considered, arguments in the Brief referring to this declaration would not be addressed herein. Furthermore, references cited in such declaration have not been considered. The Examiner will indicate instances where Appellant's arguments refer to the Bedilion declaration or those references cited in the Bedilion declaration.

In regard to arguments that the claimed polynucleotides can be used in toxicology testing, drug development, and disease diagnosis, the Examiner disagrees with Appellant's contention that these uses do not require knowledge of function to satisfy the "how to use" requirement of 35 USC § 112, first paragraph. While it is agreed that, in general, any polynucleotide, including the claimed polynucleotides, can be used to examine differential gene expression for drug discovery/development and toxicology, these

uses are enabled for a specific polynucleotide only when one of skill in the art is provided with some knowledge or guidance as to the specific diseases, conditions, and/or biological processes which are related to the expression of such polynucleotide. Since the specification does not disclose a correlation between any disease or disorder and an altered level of expression or a mutated form of the claimed polynucleotides, the results of gene expression assays would be meaningless without further research. In regard to disease diagnosis, the specification fails to disclose the specific diseases or conditions associated with the expression (or lack thereof) of naturally-occurring polynucleotides encoding proteins of any function as encompassed by the claim. Furthermore, the specification fails to disclose which are the expression levels associated with a particular disease/condition or which mutations in the claimed polynucleotides are indicative of a disease and/or condition. As such, it is unclear how the claimed polynucleotides can be used as disease markers (disease diagnosis) or as target for drug discovery or toxicology testing with the information provided by the disclosure.

1. The applicable legal standard

On page 20 of the Brief and continuing on page 22, Appellants cite case law which is allegedly relevant to the instant rejection. Appellants cite *Anderson v. Natta*, 480 F.2d 1392, 1397, 178 USPQ 458 (CCPA 1973) in support of the argument that Applicant need only show that the claimed invention is "practically useful". Furthermore, Appellants cite *Brenner v. Manson*, 383 U.S. 519, 534-35, 148 USPQ 689 (1966) in support of the argument that all is needed is a specific benefit to the public. Appellants cite *Juicy Whip Inc. v. Orange Bang Inc*, 51 USPQ2d 1700 (Fed. Cir. 1999) to indicate that the utility threshold is not high. Appellants indicate that the patent Applicant need not demonstrate utility to a certainty, citing *Stiftung v. Renishaw PLC*, 945 F.2d 1173, 1180, 20 USPQ2d 1094 (Fed. Cir. 1991), and state that if the utility is described so that one of skill in the art would understand how to use the claimed invention, it is sufficiently specific, citing *Standard Oil Co. v. Montedison*, S.p.a., 212 U.S.P.Q. 327, 343

(3d Cir. 1981). Appellants refer to *Cross v. Iizuka*, 753 F.2d 1040, 1048 (Fed. Cir. 1985) and indicate that the specificity requirement is met unless the asserted utility amounts to something that does not convey meaningful information about the utility of what is being claimed. Appellants further refer to Brenner, 383 U.S. at 534 to indicate that in addition to conferring a specific benefit to the public, the benefit must be substantial. Appellants refer to MPEP 706.03(a) to indicate that if one of skill in the art would understand that there is a well-established utility for the claimed invention, Applicant need not make any showing to demonstrate utility. Appellants cite *In re Cortright*, 165 F.3d 1353, 1357, 49 USPQ2d 1464 (Fed. Cir. 1999), *In re Brana*, 51 F.3d 1560, 1566, 34 USPQ2d 1436 (Fed. Cir. 1995), *In re Langer*, 503 F.2d 1380, 1391-92, 183 USPQ 288 (CCPA 1974), *Brana*, 51 F.3d at 1566, and *Brenner*, 383 U.S. at 532, in support of the arguments that once a patent Applicant identifies a specific utility, the PTO bears the burden of demonstrating that one of skill in the art would reasonably doubt that the asserted utility could be achieved by the claimed invention, and that Applicant need only prove a substantial likelihood of utility.

While the Examiner acknowledges the case law presented by Appellants regarding patentable utility, the essential disagreement between the Examiner's position and that of Appellants is whether or not the claimed polynucleotides, with the exception of that of SEQ ID NO: 9, are supported by a specific and substantial or well-established utility, and what constitutes a specific, substantial or well-established utility. These arguments will be addressed in detail in the following paragraphs except in those instances where the Bedilion declaration is cited.

2. Uses of the claimed polynucleotides for diagnosis of conditions and disorders characterized by expression of MITP-1, for toxicology testing, and for drug discovery are allegedly sufficient utilities under 35 USC § 101 and 112, first paragraph.

On page 22 of the Brief, first paragraph, Appellants argue that the claimed invention meets all of the necessary requirements for establishing a credible utility under the Patent Law. Appellants submit that practical specific and beneficial uses are explained in detail in the Bedilion declaration and that objective evidence not considered by the Patent Office further corroborates the credibility of the asserted utilities.

For the record, the only evidence submitted by Appellants which has not been considered is the Bedilion declaration along with the references cited by such declaration. Therefore, it is assumed that Appellant's reference to "objective evidence not considered by the Patent Office" refers only to the Bedilion declaration and its references.

a. The uses for the claimed polynucleotides for toxicology testing, drug discovery, and disease diagnosis are allegedly practical uses that confer "specific benefits" to the public.

On page 22 of the brief, second paragraph and continuing on pages 23-25, Appellants submit that the claimed invention has specific, substantial, real-world utility by virtue of its use in toxicology testing, drug development and disease diagnosis through gene expression profiling. Appellants argue that these uses are explained in detailed in the Bedilion Declaration and in the Response to Final Office Action. According to Appellants, the claimed invention is a useful tool in CDNA microarrays used to perform gene expression analysis and that this is sufficient to establish utility and enablement for the claimed polynucleotides. Appellants further indicate that the polynucleotide of SEQ ID NO: 9 was first disclosed in US provisional application No. 60/124,655, filed on 3/16/1999, and that the Bedilion declaration explains the many reasons why one of skill in the art in 3/16/1999 would have understood that the claimed polynucleotides could be useful for a number of gene expression monitoring applications, for example, in drug development, and how the claimed polynucleotides could be used in cDNA microarrays to evaluate the efficacy and toxicity of drugs as well as other applications. Appellants further argue that

the Bedilion declaration refers to extensive citations prior to 3/16/1999 showing the state of the art in regard to cDNA technology to conduct gene expression monitoring evaluations including those in drug development. As such, Appellants conclude that the Bedilion declaration provides more than sufficient reason to conclude that the claimed polynucleotides at the time of filing had substantial, specific and credible real-world utilities. Appellants indicate that the Examiner has not address the fact that the claimed polynucleotides can be used as highly specific probes in cDNA microarrays. It is Appellant's contention that the claimed polynucleotides can be used as a measuring and analyzing tool to determine expression levels and cite *Raytheon v. Roper*, 724 F.2d 951, (Fed. Cir. 1983) and *In re Cortright* 165 F.3d 1353, 1359 (Fed. Cir. 1999) in support of this argument. Appellants further cite MPEP 2107 in reference to chromatographs, screening assays and nucleotide sequencing techniques as having clear, specific and unquestionable utility.

As indicated above, arguments regarding the Bedilion declaration will not be addressed herein. In regard to arguments that the claimed polynucleotides have specific, substantial, real-world utility by virtue of their use in toxicology testing, drug development and disease diagnosis through gene expression profiling, while it is agreed that in general any polynucleotide, including the claimed polynucleotides, can be used to examine differential gene expression in applications, such as toxicology testing or drug developing, these uses are not specific and substantial for the claimed genus of polynucleotides. As indicated in MPEP 2107.01, "A 'specific utility' is specific to the subject matter claimed.". This contrasts with a general utility that would be applicable to the broad class of the invention". Polynucleotides have a variety of general uses, such as for hybridization, protein expression, and for gene expression profiling. These uses are applicable to any polynucleotide and are not specific to the claimed genus of polynucleotides. Furthermore, in regard to disease diagnosis, it is noted that this use is not specific in view of the fact that the specification is completely silent as to the specific diseases or conditions associated with the expression (or lack thereof) of naturally-occurring polynucleotides

encoding proteins of any function as encompassed by the claim. In addition, the specification fails to disclose which are the expression levels associated with a particular disease/condition or which mutations in the claimed genus of polynucleotides are indicative of a disease and/or condition.

The asserted utilities for the claimed polynucleotides in toxicology testing, drug development and disease diagnosis are not deemed substantial and "real world" utilities. As indicated in MPEP 2107.01, utilities that require or constitute carrying out further research to identify or reasonably confirm a 'real world' context of use are not substantial utilities. Since the specification fails to disclose (1) the specific diseases, conditions, and/or biological processes associated with the expression, or lack thereof, of the claimed polynucleotides, (2) a correlation between any disease or disorder and an altered level of expression or a mutated form of the claimed polynucleotides, or (3) any guidance as to how one of skill in the art should interpret results obtained from gene expression profiling in toxicology or drug development, the results of gene expression assays would be meaningless without further experimentation. Similarly, the asserted use in disease diagnosis is not deemed substantial in view of the fact that further research would be require to determine (1) the specific diseases associated with the expression, or lack thereof, of the claimed polynucleotides, and (2) the levels of expressions indicative of disease. Therefore, contrary to Appellant's assertions, the asserted utilities in toxicology testing, drug development and disease diagnosis, are not specific and substantial and do not meet the "how to use" requirement of 35 USC § 112, first paragraph.

In regard to arguments that the claimed polynucleotides can be used as highly specific probes in cDNA microarrays or as measuring tools to determine expression levels, it is noted that any polynucleotide can be part of a cDNA microarray and any coding polynucleotide can be used to determine expression levels. These uses are considered general uses and do not confer the claimed polynucleotides any specific utility. These uses are also not substantial since they would require or constitute carrying out further research to identify or further confirm a "real world" context of use.

Further research would be required in view of the fact that the specification is completely silent in regard to (1) the biological functions of polynucleotides having at least 80% sequence identity to the polynucleotide of SEQ ID NO: 9 over the entire length of SEQ ID NO: 9, with the exception of the polynucleotide of SEQ ID NO: 9, and (2) the complete absence of information as to which diseases, disorders, conditions and/or biological processes are associated with the expression, or lack thereof, of the claimed polynucleotides. In the absence of this information, measuring expression levels or using the claimed polynucleotides as probes in cDNA arrays would provide no meaningful benefit as one would not know how to interpret these results. Therefore, these uses are also not deemed sufficient to meet the "how to use" requirement of 35 USC § 112, first paragraph.

On page 25 of the Brief, second paragraph, and continuing on page 26, Appellants refer to literature reviews published after 3/16/1999. In particular, Appellants cite Rockett et al. and state that the instant reference confirms that the claimed invention is useful for differential expression analysis regardless of how expression is regulated. Appellants also refer to the teachings of Lashkari et al. in regard to the uses of predicted ORFs and how ORFs can be used directly onto glass for expression analysis.

The Examiner agrees that microarray technology, as discussed in the instant references, provides an important tool to the advancement of science. However, these references do not support the allegation that the differential expression analysis use for the claimed polynucleotides is specific and substantial or well-established so that the "how to use" requirement of 35 USC § 112, first paragraph is met. It is noted that none of the references discuss the use of specific polynucleotides, i.e. biologically characterized, in microarrays but rather discuss the generic use of any polynucleotide in microarrays. Moreover, none of these references teach the biological significance of differential expression of the claimed polynucleotides or how to interpret results regarding the differential expression of the claimed polynucleotides. As such,

the asserted utility in differential expression analysis is not deemed specific or substantial for the reasons already discussed above.

b. The use of nucleic acids coding for proteins expressed by humans as tools for toxicology testing, drug discovery, and the diagnosis of a disease is allegedly now "well-established".

On page 26 of the Brief, Appellants submit that the technologies made possible by expression profiling and the DNA tools upon which they rely are well established and cite the references of Rockett et al. (Xenobiotica 29:655), Nuwaysir et al., Steiner et al., Rockett et al. (Environ Health Perspectives 107:681), an email from Dr. Cynthia Afshari to an Incyte employee, and examples (top of page 28 of the Brief) in support of the argument that the asserted uses for the claimed polynucleotides are well-established. According to Appellants, the Examiner has failed to address or consider the "well-established" utilities for the claimed invention in toxicology testing, drug development, and disease diagnosis. As such, it is Appellant's opinion that the rejections should be withdrawn.

In regard to the argument that since the claimed polynucleotides can be used in well-established utilities such as toxicology testing, drug development, and disease diagnosis, the claimed invention has patentable utility, it is noted that for a utility to be "well-established" it must be specific, substantial and credible. In the instant case, the asserted used in toxicology testing is not specific because any expressed polynucleotide can be used to examine differential gene expression in applications such as toxicology testing. While the claimed polynucleotide can be placed in an array for toxicology screening along with many other polynucleotides, the results obtained from the array would provide no information as to each individual polynucleotide in the array since the array provides a collective expression pattern of all the polynucleotides in the array under a set of conditions. Also, as indicated above, the asserted utility in toxicology testing is not substantial since the specification fails to disclose the methods and information necessary for one of skill in the art to use the claimed polynucleotide for toxicology testing. Even if one

were to test the expression of the claimed polynucleotides in an array for drug screening, there is absolutely no guidance in the specification for interpretation of the results and the art does not provide additional information either. In the absence of any clue or guidance as to biological functions, diseases/disorders associated with expression, or lack thereof, of the claimed polynucleotides, or biological processes associated with the expression of the claimed polynucleotides, one of skill in the art would require further research to use the claimed polynucleotides as asserted. Therefore, the asserted use in toxicology testing for the claimed polynucleotides is not specific or substantial and does not constitute a well-established utility.

With regard to expression profiling for drug discovery and development, this utility is not deemed specific in view of the fact that all expressed polynucleotides can be used in expression profiling for drug discovery and development. Furthermore, in order to evaluate the efficacy of a compound from expression profiling experiments, one would require some knowledge or guidance as to (1) the condition/disease/disorder which is going to be targeted by the compound tested, and (2) how to interpret changes in expression profiling or the biological significance of those changes. At a minimum, one of skill in the art would require some knowledge in regard to the biological significance of the polynucleotide whose expression is being profiled. In the instant case, the specification is absolutely silent as to biological functions, diseases/disorders associated with expression, or lack thereof, of the claimed polynucleotides, or biological processes associated with the expression of the claimed polynucleotides. As such, one of skill in the art would require further research to use the claimed polynucleotides as asserted. Therefore, the asserted use in drug discovery and development for the claimed polynucleotides is not specific or substantial and does not constitute a well-established utility.

With regard to expression profiling for diagnosis of disease, this utility is not deemed specific in view of the fact that neither the specification nor the art provide a clue as to the specific diseases that can be diagnosed with the claimed polynucleotides. Furthermore, the specification is completely silent in

regard to (1) a correlation between the expression of the claimed polynucleotides with specific diseases, conditions, or disorders, and (2) the levels of expression or the mutated forms of the claimed polynucleotides associated with any disease or disorder. In the absence of a well known correlation or causal relationship between expression, or lack thereof, of the claimed polynucleotides and any disease or disorder, one of skill in the art would require further research and experimentation to interpret the expression profiling results and determine if there is a correlation between the claimed polynucleotides and a specific disease or disorder. "Congress intended that no patent be granted on a chemical compound whose sole 'utility' consists of its potential role as an object of use-testing." *Brenner v. Manson*, 148 USPQ at 696. Since any potential diagnostic utility is not yet known and has not yet been disclosed, the utility in diagnosis of disease is not substantial because it is not currently available in practical form and would thus require further research for its implementation. Therefore, the asserted use in diagnosis of disease for the claimed polynucleotides is not specific or substantial and does not constitute a well-established utility.

c. The similarity of the polypeptides encoded by the claimed polynucleotide variants to another polypeptide of undisputed utility allegedly demonstrates utility.

On page 28 of the Brief, last paragraph, and continuing on pages 29-30, Appellants argue that utility and enablement of the use of the claimed polynucleotides can be imputed based on the relationship between the polypeptides they encode and another of unquestioned utility, the polypeptide of SEQ ID NO: 1. According to Appellants, the more than reasonable probability that the polypeptides encoded by the claimed polynucleotides have the same utility as that of the polypeptide of SEQ ID NO: 1 is sufficient to demonstrate utility. Appellants argue that according to Brenner et al. (Proc Natl Acad Sci USA 95:6073-6078, 1998), it is well known that the probability that two unrelated polypeptides share more than 40% sequence homology over 70 amino acid residues is exceedingly small, and submit that there is

more than enough homology to demonstrate a reasonable probability that the utility of the polypeptide of SEQ ID NO: 1 can be imputed to the polypeptides encoded by the claimed polynucleotides. Appellants submit that while the Examiner has cited references (Bork, Van de Loo et al., Seffernick et al., Broun et al., Brenner (TIG 15:132-133, 1999) and Witkowski et al.) identifying the difficulties involved in predicting protein function, none suggests that functional homology cannot be inferred by a reasonable probability in this case and assert that none of the references cited contradict Brenner's rule (Proc Natl Acad Sci USA 95:6073-6078, 1998) that sequence homology in excess of 40% over 70 or more amino acids yields a high probability of functional homology. It is Appellant's contention that the standard applicable in this case is not proof of certainty but rather proof of reasonable probability. Appellants also submit that the Examiner must accept Appellant's demonstration that the homology between the claimed polynucleotides variants and the polynucleotide of SEQ ID NO: 9 is evidence of use by reasonable probability unless the Examiner can demonstrate through evidence or sound scientific reasoning that a person of ordinary skill in the art would doubt this use.

The Examiner disagrees with Appellant's contention that (1) the teachings of Brenner et al. (Proc Natl Acad Sci USA 95:6073-6078, 1998) demonstrate that one can reasonably impute the utility of the polypeptide of SEQ ID NO: 1 as a PSST subunit of the NADH:ubiquinone oxidoreductase complex to polypeptides encoded by the claimed polynucleotide variants thereof, (2) the scientific evidence by Bork, Van de Loo et al., Seffernick et al., Broun et al., Brenner (TIG 15:132-133, 1999) and Witkowski et al., presented by the Examiner does not clearly teach the unpredictability of accurately determining function based on structural homology, and (3) the standard being applied herein is certainty and not reasonable probability.

Appellant's statement in regard to how the evidence presented demonstrates that one can reasonably impute the utility of the polypeptide of SEQ ID NO: 1as a PSST subunit of the NADH:ubiquinone oxidoreductase complex to polypeptides encoded by the claimed polynucleotide

variants thereof is clearly untenable. It is without question in the art that many single amino acid substitutions within a protein result in loss of function and that the expectation of a loss of function of any polypeptide increases exponentially with each additional amino acid altered. If only the coding region of the polynucleotide of SEQ ID NO: 9 is considered (213 amino acids in SEQ ID NO: 1 = 639 nucleotides in SEQ ID NO: 9), the 80% sequence identical threshold claimed within the coding region of SEQ ID NO: 9 allows up to 128 nucleotide mismatches (0.8x639=128) and allows up to 128 amino acid substitutions in the polypeptide of SEQ ID NO: 1 (213 amino acids) if each nucleotide mismatch changes 128 different codons such that they would encode a different amino acid. Thus, the vast majority of polynucleotides having at least 80% sequence identity to the polynucleotide of SEQ ID NO: 9 will not maintain the function of the polynucleotide of SEQ ID NO: 9. While Appellant's limitation to naturally occurring sequences would reduce the number of non-functional polynucleotides encompassed (as evolution tends to naturally select against such polynucleotides), it does not eliminate them (as evidenced by the occurrence of many genetic diseases). Therefore, the claim still encompasses a large number of polynucleotides which will not share the utility of the polynucleotide of SEQ ID NO: 9. No teaching of how to use these variant polynucleotides is present. Furthermore, while a claim may include many inoperative embodiments, as is the case herein, the specification must provide guidance for the selection of the operative embodiments. In the instant case, no such guidance has been provided. Thus the scope of the claim is not commensurate with the enablement provided by the specification.

Appellants quote a portion of Brenner et al. out of context in an attempt to use these teachings to inappropriately support their argument. As indicated above and reiterated herein, the purpose of the study of Brenner et al. was to identify distant evolutionary structural homology using sequence comparison algorithms. In fact, this is asserted by Appellants on page 9 of the Brief, last line, continuing on page 10, where it is stated "The Brenner paper does not discuss predicting "functional similarity", but rather evolutionary relationships". Nowhere does the Brenner et al. reference teaches that the results obtained

can be extrapolated for use in predicting functional homology of any uncharacterized protein. Furthermore, Brenner et al. clearly states that their comparisons "have been assessed using proteins whose relationships are known reliably from their structures and functions, as described in the SCOP database" (page 6073, Abstract). The art recognizes the proteins within the SCOP database have been fully characterized, meaning their functions have been characterized by empirical laboratory experiments and their 3D structures have been generated. Therefore, the results disclosed in Brenner et al. are applicable only for identifying evolutionary homology and not functional homology, as Appellants assert. Even if one assumes that the results of Brenner et al. could be applied for functional annotation of uncharacterized proteins, it is noted that Brenner et al. teaches that the 40% identity over at least 70 residues threshold is a reasonable threshold for a database of the size and composition of that of PDB90D-B. See page 6076, right column, lines 20-26. It is reiterated herein that nowhere in the instant reference is there a statement indicating that this threshold is applicable to any set of proteins of any function. At best, one of skill in the art would conclude that the so called "Brenner's rule" is only applicable to those proteins included in the PDB90D-B database, as clearly stated in the instant reference. Therefore, the Brenner et al. reference fails to show that the homology between the claimed polynucleotides and that of SEQ ID NO: 9 is sufficient for one of skill in the art to reasonably conclude that the utility of the polypeptide of SEQ ID NO: 1 as a PSST subunit of the NADH:ubiquinone oxidoreductase complex can be imputed to polypeptides encoded by the claimed polynucleotides, as asserted by Appellants.

In regard to the scientific evidence presented by the Examiner (Bork, Van de Loo et al., Seffernick et al., Broun et al., Brenner (TIG 15:132-133, 1999) and Witkowski et al.), it is reiterated herein that it is not the Examiner's contention that sequence homology is completely unreliable and that it should never be used to make functional predictions or that all functional annotations yield incorrect results. Instead, particularly the references of Bork and Brenner (TIG 15:132-133, 1999) , were presented

to show the consensus in the art in regard to the degree of accuracy of functional annotation based on structural homology and how, with the computational tools of today and the experimental evidence available, accurate functional annotation of any protein based solely on structural homology is still unpredictable in the absence of some correlation between structure and function. The teachings of Van de Loo et al., Seffernick et al., Broun et al., and Witkowski et al. further provide experimental evidence supporting the general consensus in the art in regard to the unpredictability of the art in regard to accurate functional annotation based on structural homology as these references show that even small structural changes ranging from 1-6 amino acids result in changes in function. See discussion under Issue One, section C above, as well as the rejections under 35 USC § 112 paragraph as stated above. Since the specification provides no information as to which are the critical amino acid residues in the polypeptide of SEQ ID NO: 1 which are characteristic of PSST subunits of the NADH:ubiquinone oxidoreductase complex, and no teaching has been provided in regard to which nucleotides in the polynucleotide of SEQ ID NO: 9 can be modified such that the claimed 80% structural homologs would encode PSST subunits of the NADH:ubiquinone oxidoreductase complex, one cannot reasonably conclude that the polypeptides encoded by the claimed polynucleotides would also have the same function as that of the polypeptide of SEQ ID NO: 1.

d. Objective evidence allegedly corroborates the utilities of the claimed invention.

On page 30 of the Brief, first paragraph, and continuing on page 31, Appellants argue that "real world" utility can be demonstrated by actual use or commercial success . Appellants cite case law in support of the argument that evidence that the invention is made, use or sold by any person or entity other than the patentee is conclusive proof of utility. Appellants argue that a vibrant market has developed for databases containing all expressed genes, including those of Incyte Genomics, Inc., the real party at interest. Appellants state Incyte's customers and the scientific community have acknowledged that

Incyte's databases have been proven valuable, for example, in identification and development of drug candidates and that the databases including the claimed polynucleotide would be even more valuable as they would have an incremental benefit to the drug discovery and development process.

The case law cited by Appellants indicates that a rejection under 35 U.S.C. § 101 for lack of operability can be overcome by a showing of actual use or commercial success. In the instant case, the issue is whether or not the asserted utilities meet the three-pronged test for credibility, specificity, and substantiality. Therefore, evidence of commercial success or actual use does not provide any evidence suggesting that the claimed polynucleotides have specific, substantial or well-established utility. Many products have enjoyed commercial success due to fads or clever advertising, wherein the products would not have met the legal standards for utility under 35 USC § 101. Furthermore, while Appellants have indicated that databases sold by Incyte Genomics are commercially valuable, there is no evidence to suggest that a database is any more or less valuable with the inclusion of the claimed polynucleotide or that customers would desire to purchase the claimed polynucleotides.

3. The patent Examiner's rejections are allegedly without merit.

On page 31 of the Brief, first paragraph, Appellants argue that, rather than responding to the evidence allegedly demonstrating utility, the Examiner attempts to dismiss it altogether by arguing that the disclosed and well-established utilities for the claimed polynucleotides are not enabled. Appellants conclude that the Examiner is incorrect both as matter of law and as matter of fact.

As indicated previously, the Examiner has considered all the evidence presented by Appellants with the exception of the Bedilion declaration and references cited in that declaration, and has found no specific and substantial or well established utilities for the claimed polynucleotides. Arguments will be addressed in detail in the following paragraphs except in those instances where the Bedilion declaration or its references are cited.

a. The precise biological role or function of an expressed polynucleotide is allegedly not required to demonstrate enablement and utility.

On page 31 of the Brief, second paragraph, and continuing on page 32, Appellants assert that the Examiner's primary rejection of the claimed invention is based on the ground that, without information as to the precise biological "function" of the claimed invention, the claimed invention's enablement is not adequate. Appellants indicate that, according to the Examiner, it is not enough that a person of ordinary skill in the art could use and, in fact, would want to use the claimed invention either by itself or in a cDNA microarray to monitor the expression of genes for such applications as the evaluation of a drug's efficacy and toxicity. It is Appellant's contention that, in addition to a precise biological function, the Examiner requires a specific and substantial interpretation of the results generated in any given expression analysis. According to Appellants, while knowing the precise biological function and how to interpret results generated by expression analysis are necessary for publication in some technical journals, this is not required for obtaining a US patent. Appellants cite *In re Cortright*, 165 F.3d 1353, 1359 (Fed. Cir. 1999) and *Juicy Whip, Inc. v. Orange Bang Inc.*, 185 F.3d 1364, 1366 (Fed. Cir. 1999) in support of the argument that it is not necessary to know how the invention works as long as the invention provides an identifiable benefit. According to Appellants, the Bedilion declaration provides evidence that the present invention meets this test. Appellants refer to *Juicy Whip, Inc. v. Orange Bang Inc.*, 185 F.3d 1364, 1366 (Fed. Cir. 1999) in support of the argument that the threshold for determining whether an invention produces an identifiable benefit is low and that only those utilities which are nebulous to one of skill in the art or "throw-away" utilities not directed to a person of skill in the art, do not meet the statutory utility requirement. It is Appellant's contention that knowledge of biological function has never being required to show real-world benefit and that by requiring such knowledge, the Examiner has elevated, contrary to the law, what is at most an evidentiary factor into an absolute requirement of enablement.

Arguments related to the Bedilion declaration have not been addressed herein. With regard to the remaining arguments, it appears that Appellants have mischaracterized the Examiner's position in regard to what is required to enable the alleged uses for the claimed polynucleotides. The Examiner disagrees with Appellant's contention that she has, contrary to the law, elevated what is at most an evidentiary factor into an absolute requirement of enablement. It has not been the Examiner's position that enablement for the claimed polynucleotides requires (1) precise knowledge of biological function, and (2) specific and substantial interpretation of the results generated in any given expression analysis of these polynucleotides. The Examiner agrees that it is not required to know how an invention works, however, the alleged utilities for the claimed polynucleotides which do not required such knowledge (i.e. polynucleotides of any function comprising a naturally-occurring sequence having at least 80% identity to that of SEQ ID NO: 9 over the entire length of SEQ ID NO: 9) in toxicology testing, drug discovery and development, or diagnosis of disease, have not been found specific and substantial or well-established in view of the fact that the specification fails to disclose sufficient information such that one of skill in the art can use the claimed polynucleotides in toxicology testing, drug discovery or development, or diagnosis of disease. See particularly the extensive discussions under Issue Two, sections 2(a) and 2(b) above. The only other utility asserted, i.e. encoding a PSST subunit of the NADH:ubiquinone oxidoreductase complex, requires knowledge of how this function correlates with structure. It is reiterated herein that the specification is completely lacking in regard to the biological significance of the claimed polynucleotides, with the exception of that of the polypeptide of SEQ ID NO: 1 (encoded by the polynucleotide of SEQ ID NO: 9). There is not even a hint or clue as to which biological processes, diseases or disorder are related to the claimed polynucleotides, let alone any precise biological function. As indicated above under Issue Two, sections 2(a) and 2(b), the biological significance of the claimed polynucleotides is essential to enable uses in toxicology testing, drug discovery and development or diagnosis of disease. Without this information, these uses are not specific and substantial or well-

established for the claimed polynucleotides. Therefore, contrary to Appellant's assertion, in the instant case, some knowledge or guidance as to the biological significance of the claimed polynucleotide is required to show a "real world" benefit.

b. Membership in a class of useful products can allegedly be proof of enablement and utility.

On page 32 of the Brief, third paragraph, and continuing on page 33, Appellants argue that despite the uncontradicted evidence that the claimed polynucleotides encode polypeptides in the family of PSST subunits of the NADH:ubiquinone oxidoreductase complex and the family of expressed polypeptides, the Examiner has refused to impute the utility of the members of the family of PSST subunits of the NADH:ubiquinone oxidoreductase complex and the family of expressed polypeptides to the polypeptides encoded by the claimed polynucleotides. Appellants submit that to demonstrate utility by membership in a class, all that is required is to show that the class does not contain a substantial number of useless members. Appellants indicate that the Examiner addresses the claimed polynucleotides as if the general classes in which they are included are those comprising a vast majority of useless theoretical molecules not occurring in nature, and not the family of PSST subunits of the NADH:ubiquinone oxidoreductase complex and the family of expressed polypeptides. According to Appellants, the family of PSST subunits of the NADH:ubiquinone oxidoreductase complex and the family of expressed polypeptides are sufficiently specific to rule out any reasonable possibility that the polypeptides encoded by the claimed polynucleotides would not also be useful. Appellants argue the examiner has not presented any evidence that the family of PSST subunits of the NADH:ubiquinone oxidoreductase complex and the family of expressed polypeptides have any, let alone a substantial number, of useless members.

Contrary to Appellant's assertions, there is no uncontradicted evidence which shows that the claimed polynucleotides encode polypeptides in the family of PSST subunits of the NADH:ubiquinone oxidoreductase complex. The existence of non-functional alleles for virtually all human genes is well known in the art. Thus, limiting the genus of polynucleotides claimed to naturally occurring, does not, as argued by Appellants, assure that a polynucleotide having even 99% sequence homology to the polynucleotide of SEQ ID NO: 9 will have the same functional features. While evolution does tend to select against such non-functional alleles, it does not eliminate them. Furthermore, the 80% identity limitation is sufficiently broad such that it may include alleles of other loci as well. These alleles may have somewhat variant functions with different specificities. The scientific evidence provided by the Examiner (Bork, Broun et al., Brenner, Van de Loo et al., Seffernick et al. and Witkowski et al.), as extensively discussed in Issue One, section C and Issue Two, section 2(c), and even that provided by Appellants (Hegyi et al., Genome Research 11: 1632-1640, 2001) as discussed in Issue One, section B, clearly indicates that, as of now, with the computational tools and the experimental data available, one cannot predictably determine function of any protein based solely on structural homology. In addition, as discussed above, the specification fails to disclose (1) which are the structural elements in a polynucleotide that are characteristic of one encoding a PSST subunit of the NADH:ubiquinone oxidoreductase complex, (2) any information as to which are the structural elements in the polynucleotide of SEQ ID NO: 9 that can be altered (i.e. substituted, deleted or inserted) to create the recited structural homologs (i.e. 80% sequence identity to the polynucleotide of SEQ ID NO: 9 over the entire length of SEQ ID NO: 9) and still encode a PSST subunit of the NADH:ubiquinone oxidoreductase complex, or (3) how the structure of the polynucleotide of SEQ ID NO: 9 relates to the structure of any naturally-occurring variant as claimed so that it will encode a PSST subunit of the NADH:ubiquinone oxidoreductase complex. Thus, one of skill in the art cannot reasonably conclude that all or most of the polypeptides encoded by the claimed polynucleotides belong to the family of PSST subunits of the

NADH:ubiquinone oxidoreductase complex. While there is a probability that some of the claimed polynucleotides may in fact encode PSST subunits of the NADH:ubiquinone oxidoreductase complex, there is no indication in the specification or the art as to how many of the claimed polynucleotides encode said PSST subunits or if there is a substantial number of them which are "useless".

In regard to arguments that the claimed polynucleotides belong to the family of expressed polynucleotides, it is noted that there is no evidence to show that all the claimed polynucleotides will be expressed. Assuming arguendo that all the claimed polynucleotides are expressed, there is no evidence to show that all or most of the expressed polynucleotides have specific and substantial or well-established utilities. While it is agreed that the art teaches many expressed polynucleotides which would have patentable utility, one cannot reasonably assume that any expressed polynucleotide would have a specific and substantial or well-established utility in the absence of any teaching or suggestion as to its biological significance. Therefore, contrary to Appellant's assertions, one cannot reasonably impute utility to the claimed polynucleotides only because they belong to the family of expressed polynucleotides.

c. Because the uses of the claimed polynucleotides in toxicology testing, drug discovery, and disease diagnosis are practical uses beyond mere study of the invention itself, the claimed invention allegedly has substantial utility.

On page 33 of the Brief, last paragraph, and continuing on page 34, Appellants argue that the claimed polynucleotides, as used in toxicology testing, drug discovery and disease diagnosis, are tools and not object, of research. According to Appellants, the data generated in gene expression monitoring of the claimed polynucleotides is not used merely to study the claimed polynucleotides but rather to study properties of tissues, cells and potential drug candidates and toxins. Appellants refer to the Bedilion declaration in support of the argument that without the claimed polynucleotides, the information regarding properties of tissues, cells, drug candidates and toxins is less complete. Appellants also refer to

additional uses for the claimed polynucleotides as research tools, such as in diagnosis assays and chromosomal mapping.

Appellant's arguments, with the exception of those related to the Bedilion declaration, have been fully considered but are not deemed persuasive. In addition to the fact that many polynucleotides can be used to study the properties of tissues, cells, drug candidates and toxins, the asserted use as tools of research to study properties of tissues, cells, potential drug candidates and toxins, is not deemed specific and substantial or well-established in view of the fact that the specification is completely silent as to (1) which tissues, cells, drug candidates or toxins are being studied with the claimed polynucleotides, and (2) which properties of those tissues, cells, drug candidates or toxins are being studied. As such, the asserted use is not specific. Furthermore, the asserted use as tools of research is not substantial in view of the fact that one of skill in the art would require additional research to identify which tissues, cells, drug candidates or toxins, as well as which properties of tissues, cells, drug candidates or toxins can be studied with each one of the claimed polynucleotides. Since the specification does not provide any clue as to how one can use the claimed polynucleotides as tools of research to study properties of tissues, cells, drug candidates or toxins, one of skill in the art cannot reasonably conclude that the asserted use is specific and substantial or well-established.

In regard to arguments that the claimed polynucleotides can be used as research tools in diagnosis assays and chromosomal mapping, it is noted that these uses are also not deemed specific and substantial or well-established. The specification provides no clue as to which diagnosis assays would use the claimed polynucleotides nor does it provide any information as to which chromosomes or which regions of those chromosomes can be identified with the claimed polynucleotides. Furthermore, any human polynucleotide can be used to map its corresponding chromosome. As such, the asserted uses in diagnosis assays and chromosomal mapping are not specific. Moreover, in view of the fact that neither the specification nor the art provide any information as to (1) which diagnosis assays would use the claimed

polynucleotides, (2) how are the claimed polynucleotides used in diagnosis assays, and (3) the biological significance of those regions in the chromosome being mapped with the claimed polynucleotides so that one of skill in the art would easily recognize a "real world" utility in mapping those regions (e.g. mutations associated with disease), the asserted utilities in diagnosis assays and chromosomal mapping are not substantial because they are not currently available in practical from and it would require further experimentation to implement them. "Congress intended that no patent be granted on a chemical compound whose sole 'utility' consists of its potential role as an object of use-testing." *Brenner v. Manson*, 148 USPQ at 696. Thus, contrary to Appellant's assertions, use of the claimed polynucleotides as research tools does not meet the "how to use" requirement of 35 USC § 112, first paragraph since the asserted uses are not specific and substantial or well-established.

d. The patent Examiner has allegedly failed to demonstrate that a person of ordinary skill in the art would reasonably doubt the utility and enablement of the claimed invention: Biological function, disease association, and differential expression are irrelevant to enablement of the use of the claimed polynucleotides.

On page 34 of the Brief, second paragraph, and continuing on pages 35-36, Appellants argue that they have demonstrated a utility for the claimed polynucleotides irrespective of whether or not a person would wish to perform additional experimentation to determine biological function or biological processes associated with the claimed polynucleotides. According to Appellants, the need for additional research to determine the functionality of the claimed polynucleotides or polypeptides encoded by them is irrelevant to the utility of the invention, and assert that the Examiner is confusing use with function. Appellants further submit that they need not demonstrate whether the claimed polynucleotides are differentially expressed or associated with any disease. It is Appellant's contention that the claimed polynucleotides or the polypeptides encoded by them can be used for toxicology testing in drug discovery without any knowledge of differential expression or disease association. Appellants indicate that

monitoring of expression gives information on the potential toxicity of a drug candidate specifically targeted to other polynucleotides or polypeptides regardless of any possible utility for measuring the properties of the claimed polynucleotides or the polypeptides encoded by them. Appellants submit that changes in the expression of a particular polynucleotide by exposure to a test compound (drug candidate), and if the polynucleotide is not the target of the test compound, then these changes are indicative of undesirable toxic effects that may limit the usefulness of the drug candidate. Appellants also submit that use of a cDNA array in monitoring experiments early in the drug development process is advantageous and that indication of possible toxicity is specific to the compound tested and the polynucleotide whose expression is being monitored. Appellants conclude that contrary to the standard set forth in *In re Marzocchi*, 169 USPQ 367, 369 (CCPA 1971) the Examiner has failed to provide any reasons as to why one of skill in the art would doubt that the guidance presented in the specification would not enable one to make and use the claimed invention.

The Examiner disagrees with Appellant's contention that they have demonstrated a utility for the claimed polynucleotides irrespective of whether or not a person would wish to perform additional experimentation to determine biological function or biological processes associated with the claimed polynucleotides. On the contrary, as extensively discussed under Issue Two, sections 2(a), 2(b), and 3(a), the biological significance of the claimed polynucleotides is essential to enable uses in toxicology testing, drug discovery and development or diagnosis of disease. In the absence of information as to how to use the claimed polynucleotides in toxicology testing, drug discovery and development, or disease diagnosis, and in the absence of any teaching as to their biological role/function, specific diseases/disorders associated with their expression, or lack thereof, or expression levels or mutations in the claimed polynucleotides indicative of disease, one would not know how to use the claimed polynucleotides as asserted. In addition, in the absence of information regarding biological significance, one cannot reasonably conclude that the asserted uses are specific and substantial or well-established utilities for the

reasons already discussed under Issue Two, sections 2(a), 2(b) and 3(a). Contrary to Appellant's assertion, the Examiner is not confusing use with function since, in the instant case, some knowledge or guidance as to the biological significance of the claimed polynucleotide is required to show a "real world" context of use in toxicology testing, drug discovery and development or diagnosis of disease.

The use of the claimed polynucleotides or the polypeptides encoded by them for toxicology testing in drug discovery is not deemed specific and substantial or well-established because any expressed polynucleotide can be used to determine whether or not there are changes in its expression due to the presence of a test compound. As such, this use is not specific to the claimed polynucleotides unless there is a correlation between changes in expression of the claimed polynucleotides and a specific biological process/function, which if altered by the test compound, would result in toxic effects. Furthermore, the asserted use is also not substantial since (1) determining a correlation between changes in expression of each of the claimed polynucleotides and unknown biological processes, and (2) determining if expression changes in each of the claimed polynucleotides are indicative of toxicity, without any guidance as to the biological significance of the claimed polynucleotides would require further research to implement. In view of the fact that this use is not specific or substantial, one cannot reasonably conclude that the asserted use for toxicology testing in drug discovery is well-established.

In regard to arguments that the Examiner has failed to provide evidence showing why one of skill in the art would doubt that the guidance presented in the specification would not enable one to make and use the claimed invention, it is noted that the Examiner has provided not only scientific evidence (Bork, Broun et al., Brenner (TIG 15:132-133, 1999), Van de Loo et al., Seffernick et al., and Witkowski et al.) demonstrating that the claimed polynucleotides may encode polypeptides of unknown functions, as extensively discussed under Issue Two, section 2(c), 3(b) and Issue One, sections B and C, but has also clearly indicated why the specification does not provide sufficient guidance so that one of skill in the art can practice the full scope of the claimed invention as asserted. The Examiner has provided specific

reasons as to why the claimed polynucleotides are not deemed enabled in the Final Rejection (claim 31 was first presented in response to the Non Final Action) and the Advisory Action. In addition, the Examiner has extensively discussed why the specification does not meet the "how to make" and "how to use" requirements of 35 USC § 112, first paragraph Therefore, contrary to Appellant's assertion, the Examiner has demonstrated that Appellants have not provided sufficient guidance to enable one of ordinary skill in the art to make and/or use the invention as claimed.

For the above reasons, it is believed that the rejections should be sustained.

Respectfully submitted,

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